TRANSACTIONS OF THE AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, VOL. 111, 2000

MOLECULAR AND PATHOPHYSIOLOGIC MECHANISMS OF HYPERKALEMIC METABOLIC ACIDOSIS

THOMAS D. DUBOSE, JR

HOUSTON, TEXAS

INTRODUCTION

The co-occurrence of hyperkalemia and hyperchloremic metabolic acidosis denotes a generalized abnormality in the tubular transport of potassium and hydrogen ions. The causes of this common disorder include a large array of disorders and drug toxicities. The recent elucidation of the molecular properties of those transporters responsible for sodium absorption and potassium secretion in specialized cells of the cortical collecting duct has led, through the candidate-gene approach, to the appreciation of several inherited disorders which are often associated with hyperkalemic hyperchloremic metabolic acidosis (table 1 and figures 1, 2, and 3). Accordingly, this new knowledge has led to a better appreciation of the pathophysiology of acquired defects with similar clinical manifestations. While both inherited and acquired disorders are associated with either a direct or indirect abnormality in sodium transport in the cortical collecting tubule, the secondary varieties are more frequently associated as well with renal insufficiency and progression of renal disease. Inhibition of renal ammonium production and excretion is a major consequence of hyperkalemia, especially in the face of renal insufficiency. This results in a marked reduction in net acid excretion which further increases the severity of the acidosis. This review will focus on the interrelationships between sodium, potassium, and ammonium transport in the kidney which, when impaired, are responsible for the clinical manifestations of this common disorder.

From the Division of Renal Diseases and Hypertension, Department of Internal Medicine, University of Texas Medical School-Houston.

Reprint requests should be directed to (after January 1, 2000): Thomas D. DuBose, Jr., M.D., Chairman, Department of Internal Medicine, Kansas University Medical Center, School of Medicine, 3901 Rainbow Blvd., Kansas City, Kansas 66160-7350, Voice: (913)-588-6000, Fax: (913)-588-3995.

TABLE 1
Pathophysiologic Classification of Hyperkalemic Hyperchloremic Metabolic Acidosis

I. Mineralocorticoid Deficiency
  A. Primary
    1. Generalized (Addison's disease)
    2. Isolated (Selective) Aldosterone Deficiency
  B. Secondary
    1. Hyporeninemic Hypoaldosteronism
    2. Heparin-Induced Selective Aldosteronism Deficiency
II. Mineralocorticoid Resistance
  A. Autosomal Dominant Pseudohypoaldosteronism Type 1
III. Renal Tubular Dysfunction
  A. Voltage defects impairing K^+ and H^+ secretion
    1. Inherited
      a.) Autosomal Recessive Pseudohypoaldosteronism Type 1
      b.) Autosomal Dominant Pseudohypoaldosteronism Type 2 (Gordon's Syndrome)
    2. Acquired
      a.) Secondary to drugs which interfere with Na^+ channel function
        (1) Amiloride
        (2) Triamterine
        (3) Pentamidine
      b.) Secondary to tubulointerstitial disease which affects collecting tubule cells (Pseudohypoaldosteronism Type 3)
        (1) Obstructive uropathy
        (2) Lupus nephritis
        (3) Sickle cell nephropathy
        (4) Analgesic nephropathy
        (5) Myeloma kidney

"VOLTAGE" DEFECT IN THE CORTICAL COLLECTING TUBULE

Cell Biology and Physiology: Figure 1 represents a model of a principal cell in the cortical collecting tubule. The absorption of sodium across the apical membrane occurs through a specialized sodium channel (ENaC) (1). Transport through this highly specific apical channel is linked to the basolateral Na^+,K^+-ATPase. Operation of the sodium pump reduces the intracellular concentration of sodium, allowing sodium to flow through the selective apical channel down a favorable concentration gradient. When sodium is absorbed from tubular fluid, the translocation of the cation sodium generates a negative transepithelial potential difference. This negative voltage serves as a primary driving force for the transfer of potassium from the principal cell across the apical membrane through a specialized potassium channel (ROMK channel) (1, 2). In addition, this negative transepithelial voltage serves as a driving force for H^+ secretion by an adjacent cell, the Type A intercalated cell (not

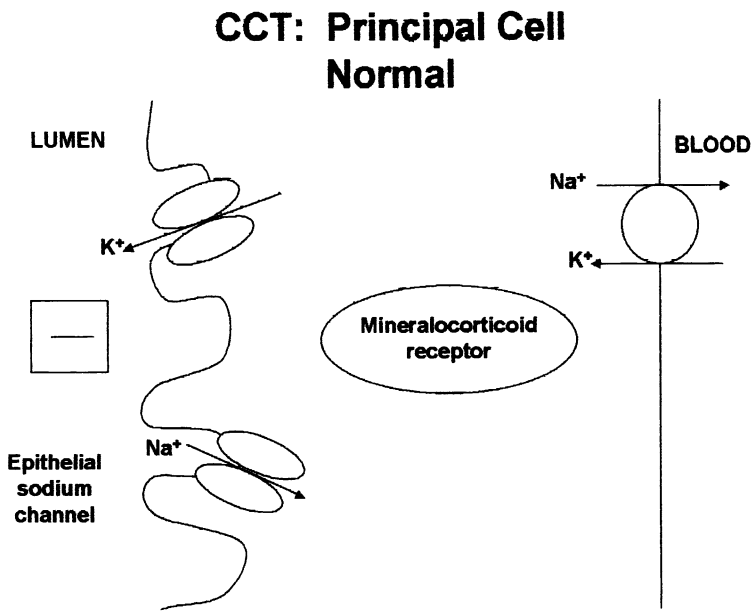

FIG. 1. Normal Principal Cell of Cortical Collecting Duct. The apical sodium channel, ENaC, is the rate-limiting barrier for Na^+ transfer across the apical membrane. The sodium pump (Na^+, K^+-ATPase on the basolateral membrane) lowers intracellular sodium to allow sodium to flow through the channel, down its concentration gradient. Operation of the Na^+ pump creates a negative transepithelial potential difference (voltage). This negative voltage drives K^+ secretion through its selective apical channel (ROMK). Mineralocorticoids regulate potassium homeostasis through their action on this cell. The type I mineralocorticoid receptor binds both aldosterone and cortisol, but not cortisone. The specificity of the receptor for aldosterone is regulated in the CCT by the kidney isoform of 11β hydroxysteroid dehydrogenase which converts cortisol to cortisone.

shown). Thus, the operation of the basolateral sodium pump, delivery of sodium in the tubule lumen to the interstitium, and the integrity of the selective sodium and potassium channels serve as important determinants of potassium and hydrogen ion transport by this segment.

Another important determinant of sodium absorption, potassium and hydrogen ion secretion in the CCT is the mineralocorticoid, aldosterone. Binding of aldosterone to its intracellular receptor within the CCT principal cell (figure 1) upregulates the activity of ENaC and ultimately the Na^+,K^+-ATPase. This bimodal effect increases the negative transepithelial voltage and thereby increases the magnitude of apical potassium and hydrogen ion secretion.

Consideration of the cell model in figure 1 reveals several mechanisms which might impair potassium secretion at this site and cause hyperkalemia: 1) inhibition of the Na^+,K^+-ATPase, 2) insufficient

function of the Na^+ channel, 3) insufficient function of the K^+ channel, or 4) an increase in Cl^- absorption (which would serve to shunt the lumen-negative potential difference). By reducing transepithelial voltage the decrease in Na^+ absorption also impairs H^+ secretion. Moreover, the development of hyperkalemia has selective effects on net acid excretion through inhibition of both ammonium production and excretion. This adverse effect of hyperkalemia further potentiates the likelihood that metabolic acidosis will accompany the hyperkalemia, especially if the hyperkalemia occurs in the face of a progressive renal functional impairment. Those disorders which are associated with inherited or acquired hyperkalemic metabolic acidosis and their clinical correlations will be discussed below.

Pseudohypoaldosteronism Type 1 (Autosomal Recessive Defect): Autosomal recessive pseudohypoaldosteronism is the result of a loss of function mutation of the epithelial sodium channel (ENaC) in the apical membrane of the cortical collecting tubule's principal cell (figure 2) (3). Four different mutations of genes which encode for one of

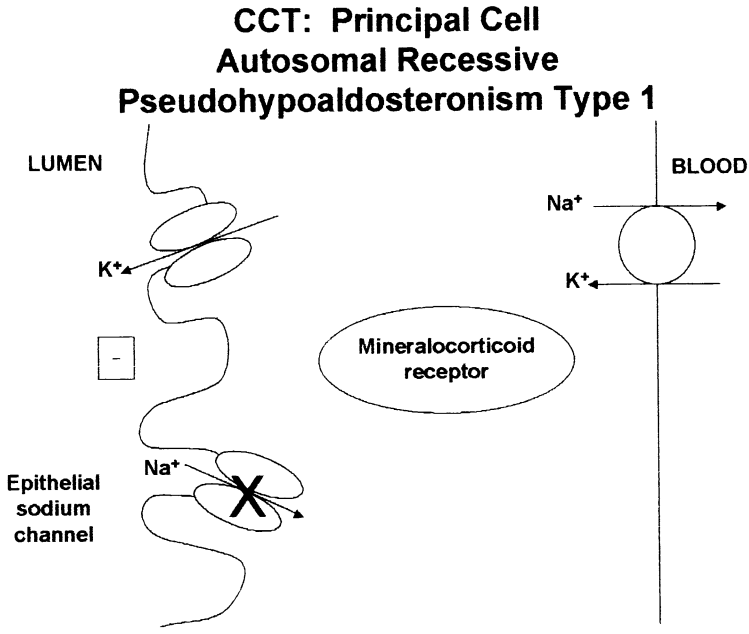

FIG. 2. Autosomal Recessive Pseudohypoaldosteronism Type 1. This disorder, a loss of function mutation of one of four genes which encode one of three subunits of this protein, impairs sodium channel function. This causes a classical "voltage" defect which inhibits K^+ secretion, in the adjoining intercalated cell, H^+ secretion (not shown). Therefore, hyperkalemic hyperchloremic metabolic acidosis develops.

the three subunits of this protein have been reported (4). All examples exhibit similar clinical features including: severe hyperkalemia, metabolic acidosis, renal salt wasting, hyperreninemia, hyperaldosteronism and a tendency toward hypotension. This autosomal recessive disorder involves multiple organ systems and the accumulation of fluid in the lung, a manifestation of abnormal sodium transport in this organ, may be especially marked in the neonatal period. These infants and small children present with vomiting, hyponatremia, failure to thrive, and respiratory distress. Patients typically respond to a high salt intake and correction of hyperkalemia.

Pseudohypoaldosteronism Type 1 (Autosomal Dominant Defect): The autosomal dominant form of this disorder (figure 3), in contrast to the recessive defect, is not expressed in other organ systems and becomes less severe with age. Four different mutations of the mineralocorticoid receptor have been reported. Carbenoxolone, an inhibitor of 11 β-hydroxysteroid dehydrogenase type II, raises the intracellular concentration of cortisol, overcomes the functional defect in the mutant receptor, and partially corrects the mineralocorticoid resistance in these patients.

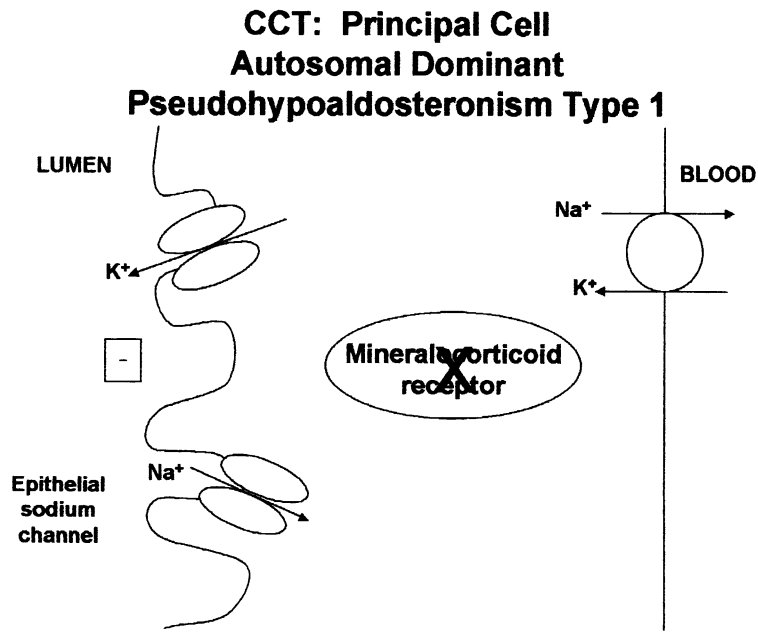

FIG. 3. Autosomal Dominant Pseudohypoaldosteronism Type 1. This defect is a defect of the mineralocorticoid receptor which impairs binding and, thereby, hyperkalemic hyperchloremic metabolic acidosis.

Pseudohypoaldosteronism Type 2 (Gordon's Syndrome): The molecular basis of this autosomal dominant disorder is unknown. It was initially assumed that because of the uniform response of patients to thiazide diuretics, this disease might represent a gain of function mutation of the neutral Na^+-Cl^- co-transporter in the distal convoluted tubule (2). Such linkage has not been established, however (1). Patients with Gordon's syndrome are hypertensive, volume-expanded and hyperkalemic with metabolic acidosis. As a result of volume expansion, both renin and aldosterone levels are low. Renal insufficiency is not an accompanying feature of this syndrome.

ACQUIRED VOLTAGE DEFECTS

Drug-induced Renal Tubular Secretory Defects:

Impaired renin-aldosterone elaboration: Drugs may impair renin or aldosterone elaboration or produce mineralocorticoid resistance (Table 2) (2). Cycloxygenase inhibitors (NSAIDs) can generate hyperkalemia and metabolic acidosis as a result of inhibition of renin release. β-adrenergic antagonists cause hyperkalemia, both as a result of altered potassium distribution and by interference with the renin-aldosterone system. Heparin impairs aldosterone synthesis as a result of direct toxicity to the zona glomerulosa with inhibition of aldosterone synthase. Angiotensin converting enzyme inhibitors (ACE inhibitors) and A II receptor antagonists can cause hyperkalemia and acidosis, particularly in the patient with advanced renal insufficiency and in patients with diabetic nephropathy. The combination of potassium-sparing diuretics and ACE inhibitors or A II receptor blockers should be avoided judiciously.

Inhibitors of potassium secretion in the collecting duct: Spironolactone acts as a competitive inhibitor of aldosterone, and may be a frequent cause of hyperkalemia and metabolic acidosis when administered to patients with renal insufficiency. Similarly, amiloride and triamterine may be associated with this disorder. Both of these potassium-sparing diuretics block the apical Na^+-selective channel in the collecting duct principal cell and alter the driving force for K^+ secretion. Drugs in this class recapitulate the inherited voltage defect of autosomal recessive pseudohypoaldosteronism type 1. Amiloride is the prototype for a large number of agents that occupy ENaC, blocking Na^+ absorption and causing hyperkalemia. Other related agents which act similarly include trimethoprim and pentamidine, particularly in patients with the acquired immunodeficiency syndrome (AIDS). Trimethoprim and pentamidine are

TABLE 2
Mechanisms of Drug-induced Hyperkalemia

I.	Impaired renin-aldosterone elaboration
	Cyclooxygenase inhibitors
	β-adrenergic antagonists
	Converting enzyme inhibitors
	Heparin
II.	Inhibitors of renal potassium secretion
	Potassium-sparing diuretics
	Trimethoprim
	Pentamidine
	Cyclosporine-A
	Digitalis overdose
	Lithium
III.	Altered potassium distribution
	Insulin antagonists (somatostatin, diazoxide)
	β-adrenergic antagonists
	α-adrenergic agonists
	Hypertonic solutions
	Digitalis
	Succinylcholine
	Arginine hydrochloride, lysine hydrochloride

related structurally to amiloride and triamterene. All of these agents are heterocyclic weak bases which exist primarily in the protonated form in an acid urine (5). The protonated forms of both trimethoprim and pentamidine have been demonstrated to inhibit the highly selective Na^+ channel in A6 distal nephron cells (2). Hyperkalemia has been observed in approximately 38% of HIV-infected patients receiving TMP-SMX or TMP-dapsone for the treatment of opportunistic infections. However, as many as 100% of patients with AIDS-associated infections receiving high dose pentamidine for more than 6 days develop this complication. Since both TMP and pentamidine decrease the electrochemical driving force for both K^+ and H^+ secretion in the CCT, metabolic acidosis frequently accompanies the hyperkalemia even in the absence of severe renal failure, adrenal insufficiency, severe tubulointerstitial disease, or hypoaldosteronism. While it has been assumed that such a "voltage" defect could explain the decrease in H^+ secretion, it is likely that hyperkalemia plays a significant role in the development of the metabolic acidosis through a decrease in ammonium production and excretion.

Cyclosporine A (CsA) may be associated with hyperkalemia as a result of inhibition of the basolateral Na^+,K^+-ATPase, thereby decreasing intracellular $[K^+]$ and the transepithelial potential. It has been suggested that the specific mechanism of CsA inhibition of the Na^+ pump is through a drug-mediated inhibition of calcineurin activ-

ity. CsA may also decrease the filtered load of K^+ through hemodynamic mechanisms, such as vasoconstriction, which decrease GFR and alter the filtration fraction.

Hyporeninemic Hypoaldosteronism: This disorder is commonly observed in patients with renal insufficiency as a result of: diabetic nephropathy, nephrosclerosis, obstructive uropathy, lupus nephritis, sickle cell nephropathy, and HIV nephropathy. For 80–85% of such patients, there is a reduction in plasma renin activity that cannot be stimulated by the usual physiologic maneuvers. The pathophysiology of the disorder in patients with diabetes mellitus is complex but may be a manifestation of infiltration or obliteration of the juxtaglomerular apparatus as well as secondary suppression of renin elaboration in response to volume expansion. The majority of these patients are hypertensive and have congestive heart failure. Lupus nephritis, through immunological assault on the cortical and medullary collecting tubule, impairs sodium transport and secondarily potassium secretion, causing hyperkalemia. Since the H^+-pump has been shown to be present in a sufficient quantity in the apical membrane of the hydrogen-secreting intercalated cell (2), it seems highly likely that the decrease in net acid secretion is the result of both a voltage-mediated reduction in net hydrogen secretion and a decrease in ammonium production and secretion in response to hyperkalemia (6). Evidence for such a defect has been deduced from both animal models of hyperkalemic acidosis from our laboratory (6–9) as well as from clearance studies in patients with clinical manifestations of this disorder. Furthermore, repair of the acidosis, upon correction of the hyperkalemia with sodium polystyrene, implies a pivotal role for hyperkalemia (see below).

Selective Aldosterone Deficiency: Selective aldosterone deficiency may be acquired frequently in critically ill patients receiving heparin. While hypoxemia, atrial natriuretic hormone, and various cytokines could play a role in the development of this disorder, most patients are receiving heparin, which inhibits aldosterone synthase (6). The clinical manifestations indicative of hypoaldosteronism include hyperkalemia, metabolic acidosis, and lack of responsiveness to ACTH infusion. Most patients respond favorably to cessation of heparin therapy.

AMMONIUM PRODUCTION AND SECRETION

Basic Physiology: The majority of ammonium excreted in the urine is derived from the metabolism of glutamine in proximal tubular cells

(10). Ammonium production in the proximal tubule is regulated through glutaminase and phosphoenolpyruvate carboxykinase activity. In states of chronic acidosis, the activities of both enzymes and the abundance of their respective messenger RNAs increase. At physiologic pH, two ammonium ions and the divalent anion, alpha ketoglutarate, are the major products of glutamine metabolism. The nephron segments responsible for ammonium transport and regulation are outlined in figure 4. Ammonium is preferentially secreted into the proximal tubular lumen across the apical membrane. Direct NH_4^+ secretion occurs via substitution of NH_4^+ for H^+ on the apical membrane Na^+/H^+ exchanger.

As tubular fluid leaves the proximal tubule, water abstraction by the thin descending limb creates a more alkaline milieu, which is favorable for ammonia (NH_3) efflux (figure 4). Direct NH_4^+ transport across the TALH apical membrane by substitution of NH_4^+ for K^+ on the Na^+-$2Cl^-$-K^+ cotransporter is a major mechanism for absorption and is responsible for generation of high medullary ammonium concentrations. A highly selective K^+ channel which is sensitive to ATP

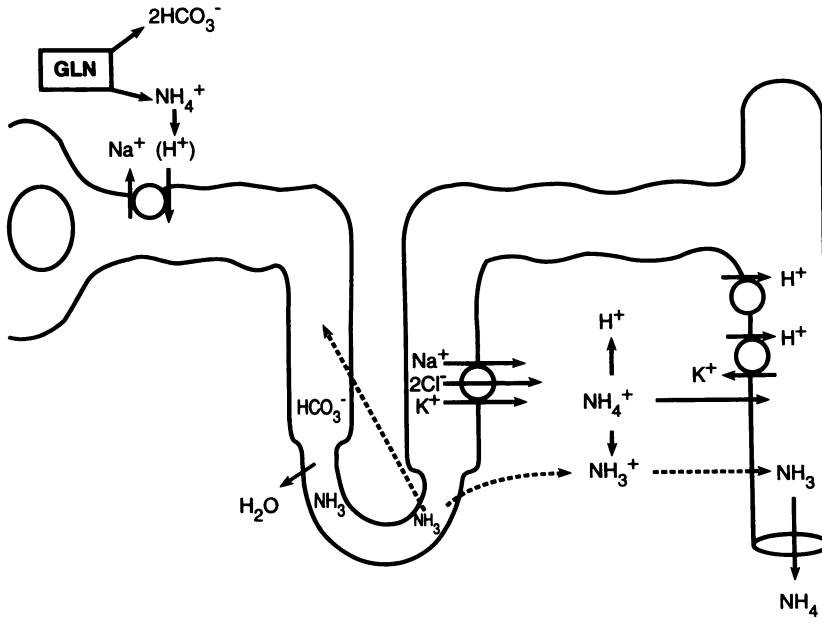

FIG. 4. Nephron segments responsible for ammonium excretion. Ammonium excretion is regulated in response to changes in systemic acid-base and potassium homeostasis. Segmental contributions include: proximal convoluted tubule, proximal straight tubule, thin descending limb, thick ascending limb, and medullary collecting duct. See text for explanation. Gln = glutamine.

(ROMK-2) has been cloned and localized to mTALH and could represent a channel which is responsible for NH_4^+ exit across the basolateral membrane of the mTALH.

Ammonia can re-enter the proximal straight tubule from the interstitium, thus leading to countercurrent multiplication whereby the "single effect" involves selective addition of ammonium by the proximal tubule and active ammonium absorption in the thick ascending limb of Henle's loop. The countercurrent system in the loop then multiplies the effect. The net result of this system is an axial gradient for ammonium: medullary concentrations of NH_4^+ exceed cortical concentrations by several-fold. The concentrations of NH_4^+ and NH_3 in the medullary interstitium exceed the concentration prevailing in the medullary collecting duct lumen. Thus, a concentration gradient favorable for entry into medullary collecting duct is created. Ammonium concentrations in the inner medullary interstitium reach greatest amplification over cortical levels during chronic metabolic acidosis. Medullary washout and selective medullary destruction (e.g. chronic tubulointerstitial diseases) can obliterate the hyperammoniagenic environment of the inner medulla.

Ammonium is secreted from the medullary interstitium into the medullary collecting ducts by a combination of NH_3 diffusion and active H^+ secretion (H^+-ATPase and the H^+,K^+-ATPase) resulting in high concentrations of ammonium in final urine. In addition, Susan Wall in our Division has recently demonstrated that ammonium entry into the tIMCD cell on the basolateral membrane is accomplished by competition of NH_4^+ for K^+ on the sodium pump (Na^+,K^+-ATPase) (11).

Metabolic acidosis increases ammonium production through stimulation of glutaminase and phosphoenolpyruvate carboxykinase in the proximal tubule (10). Moreover, in chronic metabolic acidosis, net ammonium addition to the proximal tubule is increased through augmentation of ammonium secretion (10). In response to the increase in delivery out of the late proximal tubule, ammonium absorption by the thick ascending limb of Henle's loop is augmented, thus increasing inner medullary interstitial concentrations of ammonia (NH_3). As a consequence of inner medullary accumulation of ammonia and the increase in the activity of the H^+-pump in the inner medullary collecting duct, ammonium addition to the medullary collecting duct and thus net acid excretion increases.

Clinical Correlation: The regulatory response by the kidney to chronic metabolic acidosis is to increase ammonium production and excretion. Therefore, in a patient with chronic metabolic acidosis of

non-renal origin an increase in ammonium excretion is anticipated. Renal tubular disorders such as the renal tubular acidoses are associated with an inappropriately low ammonium excretion rate when the degree of systemic acidosis is taken into consideration. The urine anion gap, or the urine net negative charge, has been applied as a clinical means to estimate the response of urinary ammonium excretion to metabolic acidosis. Hyperchloremic metabolic acidosis due to gastrointestinal losses can be differentiated from a renal tubular defect, since urinary NH_4^+ excretion is typically low in renal tubular abnormalities and high in patients with extrarenal bicarbonate loss (e.g. diarrhea).

TREATMENT OF HYPERKALEMIA AND METABOLIC ACIDOSIS

Reduction in serum potassium will often improve the metabolic acidosis by increasing ammonium excretion as potassium levels return to the normal range. Patients with hyporeninemic-hypoaldosteronism may respond to a cation exchange resin (sodium polystyrene sulfonate), alkali therapy, or treatment with a loop diuretic to induce renal potassium and salt excretion. Supraphysiologic doses of mineralocorticoids may be necessary but should be administered cautiously in combination with a loop diuretic to avoid volume overexpansion or aggravation of hypertension and to increase potassium excretion. Children with pseudohypoaldosteronism type 1 should receive salt replacement aggressively, and the hyperkalemia corrected with exchange resins. Carbenoxolone may be useful in children with autosomal dominant pseudohypoaldosteronism type 1. Patients with pseudohypoaldosteronism-type II should receive thiazide diuretics along with dietary salt restriction.

SUMMARY

In summary, hyperkalemia may have a dramatic impact on ammonium production and excretion. Chronic hyperkalemia decreases ammonium production in the proximal tubule and whole kidney, inhibits absorption of NH_4^+ in the mTALH, reduces medullary interstitial concentrations of NH_4^+ and NH_3, and decreases entry of NH_4^+ and NH_3 into the medullary collecting duct. The potential for development of a hyperchloremic metabolic acidosis is greatly augmented when renal insufficiency with associated reduction in functional renal mass coexists with the hyperkalemia, or in the presence of aldosterone deficiency or resistance. Such a cascade of events helps to explain, in part, the hyperchloremic metabolic acidosis and reduction in net acid

excretion characteristic of several experimental models of hyperkalemic-hyperchloremic metabolic acidosis including: obstructive nephropathy, selective aldosterone deficiency, and chronic amiloride administration (7,9).

ACKNOWLEDGMENTS

Some of the observations discussed in this paper were generated by original studies in the author's laboratory and were supported by a grant from the NIDDK: DK30603-17. The author acknowledges the superb secretarial support of Marla Lampp.

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DISCUSSION

CAREY, Charlottesville: I was very interested in your finding that hyperkalemia has an effect on ammonia transport and formation. Does this finding relate specifically to hyporeninemic hypoaldosteronism, the most common form of hyperkalemic disorders? Do we know that specifically?

DuBOSE: Bob, no, we do not because there is not a good animal model. Clearance studies that have been done in patients with hyporeninemic hypoaldosteronism have

included a wide spectrum of patients, many that have more advanced renal disease than others, so they have been difficult to study. The clearance studies done by Dan Battle suggest that since all of these patients have low ammonium concentrations in the urine, which correlates inversely with the degree of hyperkalemia. It likely is related, just as we see in the available animal models. This is the same that we have observed.

CAREY: Are there any therapeutic implications of these findings for the relationship between hyperkalemia and ammonia metabolism?

DuBOSE: Absolutely. I think that is a very good point. With correction of chronic hyperkalemia in many of these patients, the metabolic acidosis will be ameliorated. This was shown by Sylzman in the *New England Journal* some years ago. We find that this is often not done, but when it is done, it is usually quite successful.

LUKE, Cincinnati: Tom, thank you for that exposition of modern nephrology to which you have contributed a great deal. Two questions. One, the Thailand story and vanadium inhibition of the H^+,K^+-ATPase, what do you think about that? Second, the autoimmune disorders like Sjogren's where antibodies to the H^+-ATPase have failed to localize the pump in the apical membrane of the collecting tubule. Are these real in your view? How do they fit in?

DuBOSE: The biopsy results from Gluck, Solemani and others represent the best evidence that in acquired forms of classical distal RTA, the H^+-ATPase is defective or is not inserted into the apical membrane of the collecting duct. Insofar as the vanadium story goes, this potential environmental toxin has been proposed as a cause of hypokalemic distal RTA, which is quite prevalent in Thailand. Vanadate is an inhibitor of all P-type ATPases and is not specific to the H^+,K^+-ATPase. Furthermore, there is a very high incidence of hypokalemia in northeastern Thailand. The association between vanadium and distal RTA appears to be fortuitous. It appears that this disorder is a result of severe chronic hypokalemia that causes kaliopenic nephropathy and, therefore, an acidification defect due to medullary washout. There has really been no direct link to vanadium. This is a very significant public health problem there because severe hypokalemia occurs in impoverished groups that have a very low amount of potassium in the diet, and the number of deaths attributable to hypokalemia is significant.